PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P.HENO.04B/WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/03245	International filing date *(day/month/year)* 20.06.2003	Priority date *(day/month/year)* 21.06.2002
International Patent Classification (IPC) or both national classification and IPC A61L26/00		
Applicant HENOGEN S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.01.2004	05.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Winger, R Telephone No. +49 89 2399-8129

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/03245

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-22 as originally filed

Claims, Numbers

1-12 received on 18.08.2004 with letter of 11.08.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/03245

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 12 (industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 12 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,3
	No:	Claims	1,4-12
Inventive step (IS)	Yes:	Claims	
	No:	Claims	2,3
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Section III

1. Claim 12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Section V

2. Prior Art: Reference is made to the following documents cited in the International Search Report

   D1: WO 01/45760 A
   D2: WO 97/29792 A
   D3: DATABASE EMBASE [Online] ELSEVIER 'SCIENCE PUBLISHERS, AMSTERDAM, NL; 1982, VAN DEN BESSELAAR A M H P ET AL: "The role of factor IX in tissue thromboplastin induced coagulation"
   D4: ACIL YAHYA ET AL: "Effects of bone morphogenetic protein-7 stimulation on osteoblasts cultured on different biomaterials" JOURNAL OF CELLULAR BIOCHEMISTRY, vol. 86, no. 1, 2002, pages 90-98

2.1 Document D1 discloses a sealant / bone generating product comprising platelet rich plasma, a growth factor (INNOVIN = thromboplastin + phospholipid) and bone particles (protein scaffold). The bone particles are preferably not denatured and thus comprise collagen.

2.2 Document D2 discloses a sealant comprising thromboplastin, collagen, factor VII, and plasma in the form of a single- or dual-component composition. The thromboplastin is always lipidated (either naturally or artificially) and may be for example Innovin. Optional components are therapeutic agents including antibiotics. The sealants are known to be osteogenic or osteostimulatory.

2.3 Document D3 discloses studies on the clotting times of various deficient plasmas using active thromboplastin in the presence of factor VII.

2.4 Document D4 discloses that stimulation of biomaterials such as PepGen p-15 with rhBMP-7 increases cell proliferation and collagen synthesis and might lead to an enhanced osseointegration of the biomaterial in vivo.

3. Novelty (Article 33(2) PCT):

Claim 1 relates to a (tissue generating) product comprising a plasma matrix, one or more growth factors, at least one phospholipid and a protein scaffold selected from a matrix of collagen, reticuline and/or elastine fibers or their precursors. However, as such compositions are disclosed in documents D1 and D2, the subject-matter of claims 1, 4, 5 and 6 (composition not distinguished by technical feature) is not novel. For the same reason the subject-matter of claim 7, relating to a kit for the preparation of said tissue generating product, claims 8-10, relating to a method for the preparation, claim 12, relating to a method of tissue generation and claim 11, relating to the manufacture of a medicament is not novel.

4. Inventive Step (Article 33(3) PCT):

Document D1, which is considered to represent the closest prior art, differs with respect to the protein scaffold (claim 2) and the plasma (claim 3) used.
The problem to be solved can be regarded as to provide an alternative tissue generating product.
However, the solution proposed in claim 2, namely the selection of a collagen precursor instead of collagen seems to be obvious for the skilled person and, therefore, not inventive.
The solution proposed in claim 3, namely the selection of platelet poor plasma, is not considered inventive, as no effect seems to be associated with such an (arbitrary) selection. The examples are all carried out with PRP.

5. Industrial Applicability (Article 33(4) PCT):

For the assessment of the present claim 12 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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NEW SET OF CLAIMS

1. A tissue-generating product comprising a plasma matrix, one or more growth factors, at least one phospholipid and a protein scaffold for the generation of said tissue wherein the protein scaffold is a matrix of collagen, reticuline and/or elastine fibers or their precursors.

2. The tissue-generating product acc to claim 1, wherein the precursor is the tropocollagen or the tropoelastine.

3. The tissue-generating product according to claim 1 or 2, wherein said plasma matrix is a coagulated matrix of platelet poor plasma comprising a platelet concentration lower 500,000, 100,000 or 50,000 platelets per microlitre of the matrix forming agents.

4. The tissue-generating product according to any of the preceding claims, wherein the growth factor is selected from the group consisting of the human (recombinant) tissue factor (rhTF), the human (recombinant) platelet-derived growth factor (rhPDGF), the human (recombinant) transforming growth factor (rhTGF), the human (recombinant) insulin-like growth factor (rhIGF), the human (recombinant) epidermal growth factor (rhEGF) or the human (recombinant) hepatocyte growth factor (rhHGF).

5. The tissue-generating product according to any of the preceding claims, which further comprises at least one buffer and at least one antibiotic.

6. The tissue generating product according to any of the preceding claims, wherein the tissue is skin or an epithelial tissue of the stomach.

7. A kit for the preparation of a tissue generating product according to any of the preceding claims, which contains a vial containing human growth factors, the protein scaffold elements (which are selected from the group consisting of collagen, reticuline and/or elastine fibers or their precursors) or two distinct vials, a first containing one or more growth factors, while the second vial containing protein scaffold elements selected from a group consisting of collagen, reticuline, and/or elastine fibers or their precursors, and possibly a last vial which may contain at least one buffered agent and at least one antibiotic.

8. A method for the preparation of a tissue generating product according to any of the claims 1 to 6, in which:

- a substantially homogenous mixture is formed by mixing a plasma matrix with an effective amount of protein scaffold elements selecting from the group consisting of collagen, reticuline and/or elastine fibers or their precursors;
- a growth factor and at least one phospholipid are added and mixed to the mixture of the protein scaffold elements and the plasma matrix, and
- the said mixture is kept under conditions for ensuring the coagulation of the plasma matrix and the formation of the tissue generating product.

9. The method according to claim 8, wherein the coagulation of the matrix in carried out in the presence of oxygen and substantially without stirring.

10. The method according to claim 8 or 9, wherein the coagulation is carried out at a temperature comprised between 35° and 40°C, more preferably at a temperature of about 37°C.

11. Use of the tissue-generating product according to any of the claims 1 to 6, for the manufacture of a medicament in the treatment of tissue damages in a mammal patient, including the human.

12. A method for generating a tissue in a mammal patient, including the humans in need thereof, said method comprising the step of applying at the place where the tissue has to be generated the generating product according to any of the claims 1 to 6.